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Cardiovascular outcomes after domino liver transplantation

Alterações cardiovasculares após transplante hepático sequencial

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RESUMO

Introdução e objetivos

O transplante hepático sequencial (THS) consiste na utilização de fígados excisados de doentes com amiloidose por transtirretina (ATTR) hereditária como enxertos para outros doentes com patologias hepáticas graves e com prognóstico reservado.

O nosso objetivo era investigar o desenvolvimento de manifestações cardíacas de amiloidose por transtirretina iatrogénica (ATTRi) em doentes com THS.

Métodos

Analisámos retrospetivamente os dados clínicos e exames de 72 doentes consecutivos submetidos a THS entre 2007 e 2010 no nosso centro, que receberam fígados com mutação V30M.

Resultados

A nossa amostra tinha 79% de homens, idade mediana aquando do transplante de 56 anos, com mediana de tempo de seguimento de 80 meses (IQR 21-101).

Após uma mediana de 17 meses, 44% morreram. Manifestações de ATTRi ocorreram em 29%, em média 6 anos após THS; em 76% dos doentes nos quais foi realizada biópsia foi detetada amilóide.

Alterações significativas da condução cardíaca foram raras (apenas 1 doente); contudo, verificou-se uma tendência aumentar o intervalo PR e ocorreu fibrilhação/*flutter* auricular em 8%.

Sinais de envolvimento miocárdico foram relativamente mais frequentes, nomeadamente aumento da espessura miocárdica com fração de ejeção preservada. Desenvolveu-se presumível miocardiopatia infiltrativa em 9 casos (12,5%), após uma mediana de 68 meses (IQR 26-96).

Conclusões

Os doentes que fizeram THS tiveram mortalidade considerável, ocorrendo ATTRi mais frequentemente e precocemente do que esperado. Um padrão de miocardiopatia infiltrativa foi mais comum e alterações da condução mais raras do que seria previsível a partir de dados de ATTR V30M hereditária.

Palavras-chave: Transplante hepático sequencial; amiloidose; condução elétrica cardíaca; miocardiopatia infiltrativa; insuficiência cardíaca.

ABSTRACT

Introduction and purpose

Domino liver transplantation (DLT) is a procedure that uses the livers excised from patients with hereditary transthyretin-related amyloidosis during liver transplantation as grafts to other patients with severe hepatic pathologies and a reserved prognosis.

Our aim was to investigate the development of cardiac manifestations consistent with iatrogenic transthyretin amyloidosis (iATTR) in recipients of DLT.

Methods

We retrospectively analyzed the medical records and exams of 72 consecutive patients submitted to DLT between 2007 and 2010 in our centre, who received livers with V30M mutation.

Results

Our sample had 79% male patients, median age at transplantation of 56 years and median follow-up time of 80 months (IQR 21-101).

After a median of 17 months, 44% of the patients died. Manifestations of iATTR occurred in 29%, on average 6 years after DLT, and amyloid was seen in 76% of those who underwent a biopsy.

Significant conduction changes were rarely seen (present in 1 patient); however there was a trend towards an increase in PR interval and atrial fibrillation/ flutter was reported in 8%.

Signs of myocardial involvement were relatively more common, namely increased wall thickness with preserved ejection fraction. Presumed infiltrative cardiomyopathy was found in 9 cases (12.5%), after a median of 68 months (IQR 26-96) after DLT.

Conclusions

Patients that underwent DLT had a considerable mortality rate and iATTR occurred more frequently and earlier than expected. A pattern of infiltrative cardiomyopathy was relatively more common and conduction disorders rarer than one would extrapolate from hereditary ATTR V30M data.

Key-words: Domino liver transplantation; amyloidosis; cardiac electric conduction; infiltrative cardiomyopathy; heart failure

ABREVIATURAS

ATTRi - Amiloidose por Transtirretina Iatrogénica
THS - Transplante Hepático Sequencial

ABBREVIATIONS

ATTR - Hereditary transthyretin related amyloidosis
AV - Atrioventricular
DLT - Domino Liver Transplantation
FAP - Familial Amyloid Polyneuropathy
iATTR - Iatrogenic Transthyretin Amyloidosis
LT - Liver Transplantation
LV - Left Ventricular
TTR – Transthyretin

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INTRODUCTION

Hereditary transthyretin related amyloidosis (ATTR) is an autosomal dominant disease caused by extracellular deposition of mutated transthyretin, forming amyloid fibrils due to destabilization of the tetramer.[1-5] Although more than 100 different mutations in transthyretin (TTR) have been described, the most common is V30M.[2, 5, 6] There is an endemic area of early onset disease in the north of Portugal, with ATTR V30M mutation (V50M in the new nomenclature),[7] characterized by slowly progressive sensory-motor peripheral and autonomic neuropathy [1-4, 6, 8] and designated as Familial Amyloid Polyneuropathy (FAP). Centro Hospitalar do Porto is a reference centre for the treatment of this disease and even though the hallmark manifestation of TTR-FAP is neurological, it may also have cardiovascular, gastrointestinal, ophthalmologic, renal and urological manifestations.[2-4, 8]

Transthyretin is mainly produced by the liver [1, 3, 4, 9-11] – in spite of being also formed in the retinal pigment epithelium and in the choroid plexus in small quantity [12, 13] - and liver transplantation (LT) emerged as the first effective treatment of the disease, which may detain its progression.[2, 3, 9-11] On the other hand, orthotopic liver transplantation is also frequently used in the treatment of severe liver diseases. [10]

Since one of the major limitations of LT is the shortage of organs for transplantation, the livers excised from TTR-FAP patients during LT began to be used for transplantation of other patients with severe hepatic pathologies and a reserved prognosis (who would therefore not be candidates for LT). Considering that the liver of a patient with TTR-FAP is anatomically and functionally normal, except for producing mutated transthyretin, [14] it was presumed that a proportion of the recipients would never present the disease or that it would take decades before the first manifestations of systemic amyloidosis – since patients usually have symptoms of the disease from the third decade of life onwards. This process is called sequential or domino liver transplantation (DLT) [3, 4, 10, 15]and was first performed in 1995 in Portugal. [15-17]

This surgery has increased the supply of hepatic grafts that could be used in transplantation and enabled the treatment of older individuals or patients with a worse prognosis who would not be transplanted. [18] In addition, it has the advantage that donors are generally young and the time of ischemia is shorter. Thus, in some centres the criteria for DLT have been broadened.[2, 3, 8, 10, 19]

However, few studies have evaluated the long-term results of DLT and some published cases have shown that the manifestations of acquired or iatrogenic transthyretin-related amyloidosis (iATTR) are not always as late as anticipated.[2, 4, 9, 14, 20, 21]

Cardiac amyloidosis may or may not be related with systemic impairment[22, 23]. In patients with a non-cardiac biopsy presenting amyloid deposition, cardiac involvement is usually defined as either a positive heart biopsy, unexplained low voltage on the ECG and/or increased left ventricular wall thickness (an interventricular septal thickness $\geq$12 mm, in the absence of hypertension or other potential causes of left ventricular hypertrophy). [23, 24]
The main manifestations of cardiovascular disease in these cases are the conduction disorders, such as sinus node disease, atrioventricular (AV) blocks and intraventricular conduction delays or bundle branch blocks, which may require permanent pacemaker.[25] However, myocardial infiltration with amyloid is also frequently present. Typical abnormalities involve increased right and left ventricular wall thickness with normal cavity size, diastolic dysfunction, as well as the progressive thickening of the atrial septum, increased myocardial echogenicity, valve thickening and pericardial effusion.[26-28] Left ventricular (LV) systolic impairment is rare and a typical pattern of relative apical sparing of longitudinal strain has been described. [29] There were also found common some electrocardiographic features as low voltage, pseudo-infarction pattern, poor R wave progression in the precordial leads and arrhythmias, including atrial fibrillation and flutter.[22, 23, 26, 30]

The development of congestive cardiac failure is possible, and death can ensue within 6 months.[23]

Our aim is to describe the development of cardiac manifestations consistent with iatrogenic TTR amyloidosis (iATTR) in patients that underwent DLT and received the liver of a patient with TTR-FAP. We will evaluate the occurrence of changes in the electric conduction system of the heart and myocardium involvement, namely development of heart failure and features of an infiltrative cardiomyopathy. We intend to analyze the occurrence of iATTR, the timing of these manifestations and the prognosis of these patients.

METHODS

This is a retrospective observational study that includes 72 patients submitted to DLT at Centro Hospitalar do Porto (Porto, Portugal), between January 2007 and December 2010. They received livers from patients with hereditary ATTR caused by V30M mutation.

We collected demographic information, clinical characteristics, laboratorial and imaging data, through consultation of the clinical information and exams.

This study was approved by our centre's ethical committee (N/REF.ª 2018.023(022-DEFI/022-CES).

Statistical analyses

Continuous data are described as mean ± standard deviation or median (25-75 interquartile range) for non-gaussian distributions. Categorical data are presented as absolute frequencies (n) and percentages.

Continuous variables were compared using *t* test or Mann-Whitney U test, as appropriate, and categorical variables using Fisher's exact test.

The intra-individual comparison of parameters during follow-up was done using *t* paired-sample test or Wilcoxon signed-rank test, or McNemar test for categorical variables.

We used SPSS® software, version 23, considering $p<0.05$ for statistical significance.

RESULTS

We included 72 patients submitted to DLT at our centre; 79% (n=57) were male, with a median age at transplantation of 56 years (IQR 50-60; range 54-72) – Table 1.

The most common reasons for undergoing liver transplantation were: alcoholic cirrhosis (44%), hepatocellular carcinoma (31%) and chronic liver disease nonalcoholic and nonviral (10%).

During a median follow-up time of 80 months (IQR 21-101), 44% (n=32) died, after a median of 17 months (range 0 to 106 months).

A fatal complication (directly or not) related to the transplant occurred in 32% of the patients, whereas 29% had a nonfatal complication.

As per the medical records, 8 patients were considered for re-transplantation: 3 were retransplanted (1 because of amyloidosis and 2 because of graft dysfunction) and 5 were in the waiting list.

Iatrogenic ATTR was diagnosed in 21 patients (29%), 68 ± 25 months after DLT (median 71, range 20 to 110 months).

Of the 43 patients that underwent a biopsy, it was positive for amyloid in 33 cases (46% of the total), on average 56 ± 13 months after DLT (range 30 to 86 months). Most biopsies were of the salivary glands, that are used routinely at our centre.

Neurological symptoms of iATTR were reported in 20 patients, on average 68 ± 27 months after DLT. In 10 patients, gastrointestinal symptoms were present, urologic symptoms in 3, ophthalmologic in 2 and renal also in 2 patients. In most patients (n=20), the first symptoms of iATTR were neurological.

In terms of potential confounders, 33 patients had diabetes or another possible cause for peripheral neuropathy.[14, 17, 21, 31]

- **Electric conduction changes**

Significant conduction changes (second degree Mobitz II or third degree AV block; symptomatic sinus node disease or another general indication for pacemaker implantation) [30, 32-35] were reported in just one patient (that died before pacemaker implantation).

A permanent pacemaker was implanted in 2 patients, in both cases “prophylactically” before re-transplant.

Bradycardia, defined as heart rate < 50 bpm, was registered in 7 patients.

Atrial fibrillation or flutter occurred in 6 patients (8%), no other supraventricular or ventricular arrhythmias were reported (Table 2).

Between baseline and 6 years of follow-up, the PR interval significantly increased and the voltage in the precordial leads (measured as Sokolow index) decreased – Table 2.
Pathological Q waves, repolarization changes and poor R wave progression in the precordial leads were frequently seen (Table 2).

- **Myocardial involvement**

Myocardial involvement of iATTR (Table 3) was assumed in 9 patients (12.5%), on average 65 ± 35 months after DLT (median 68; IQR 26-96): 3 had a phenotype of cardiac amyloidosis and symptoms of heart failure, 4 had heart failure symptoms without a milder phenotype, 2 had phenotypic changes without evident heart failure symptoms. An additional patient had phenotypic changes suggestive of heart failure before DLT.
Of the 55 patients that had records of an echocardiogram at baseline, 22 had increased wall thickness (≥12 mm). Of the 26 that repeated echo, 17 (65%) had increased wall thickness; 7 of those had normal wall thickness at baseline. There was a non-significant trend towards an increase in wall thickness (p= 0.077).
Only 1 patient had compromised LV systolic function, already present pre-transplant, and died with acute transplant complications.
ProBNP levels did not significantly change during follow-up (Table 4).
In terms of potential confounders for interpreting LV wall thickness and proBNP levels, it is important to consider that during follow-up 28 patients had hypertension and 28 had chronic kidney disease.

DISCUSSION & CONCLUSIONS

A significant proportion of the DLT recipients developed manifestations of iATTR: 29% were formally diagnosed with iATTR, on average 6 years after DLT. Moreover, in 76% of those that had a biopsy, it was positive for amyloid, which is in line with other studies that claim that deposition of amyloid, for example in the GI tract and skin as well as in the salivary glands, can precede clinical symptoms. [36-38] So even if the symptoms were not clear-cut, we can consider that tissue involvement was present in all those patients, on average 5 years after DLT.

In what concerns cardiovascular involvement, disturbances of the electrical conduction system were rare, but could possibly be detected with a longer follow-up and systematic examinations. Significant conduction changes were reported in just one patient; bradycardia occurred in 10% and 2 patients implanted a “prophylactic” pacemaker. Atrial fibrillation or flutter was registered in 8% of our sample.

Signs suggestive of myocardial involvement were not uncommon after LT, namely increased wall thickness during follow-up and probable infiltrative cardiomyopathy was seen in 9 cases (12.5%). The definitive diagnosis of cardiac amyloidosis is often difficult to make in these patients, especially since the hallmark of increased wall thickness and diastolic dysfunction can also be related to other factors such as aging and hypertension. [39] In this regard, cardiac magnetic resonance, ^{99m}Tc-DPD (99m technetium labelled 3,3-diphosphono-1,2-propanodicarboxylic acid) scintigraphy, 123-iodine metaiodobenzylguanidine (MIBG) imaging, advanced echocardiographic analysis using strain and endomyocardial biopsy can be particularly useful, even though they were not routinely used in our sample.

As we could understand from the data, after evident clinical symptoms and amyloid deposition was proved, some patients underwent retransplantation. The aim of this surgery is based in the multiple evidence that LT can stop the progression of the hereditary disease. Yet, several studies have shown that conduction changes and cardiomyopathy caused by amyloid deposition are not reversible by LT and continue to develop after liver transplantation in patients with hereditary amyloidosis, and heart transplantation is rarely a possibility. [23, 26, 39, 40]

The concept that iATTR would manifest only around 25-30 years after DLT was proven wrong, possibly because of epigenetic and aging factors that are involved in amyloidogenesis. In fact, some articles demonstrate that the advanced age of the recipient can be a cause of early *de novo* amyloid deposition in the tissue. It was also observed more

severe deposition in these patients. However, the possibility that part of this amyloid deposition is due to wild-type TTR, which is common in elderly people, is not excluded.[8, 37] Nevertheless, DLT can be a valid option for patients that are not candidates for LT or with a very poor short-term prognosis. [8, 21, 37, 41] When DLT was first described, only one patient had survived more than 5 years [16]; in our sample, 46 patients (64%) survived more than 5 years.

The risks and benefits of DLT and the expected course of iATTR should be thoroughly discussed with the patients and we recommend that they are followed by a multidisciplinary team that would perform at least a neurologic and cardiologic assessment, at baseline and every year after transplantation (since iATTR can manifest itself 20 months after DLT).

Our study has several limitations, essentially due to its retrospective and observational design; the small sample size and missing data did not allow us to properly analyse several parameters, such as echocardiographic data, troponin or proBNP levels. Data from Holter monitoring was also rare.

This study highlights the importance of a systematic follow-up of these patients, what can help us to better understand and intervene on iATTR, and possibly will also enlighten our understanding of hereditary ATTR amyloidosis.

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DISCLOSURE OF INTEREST

The authors have no conflicts of interest.

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TABLES

Table 1 - Study sample characterization

Age at transplantation; median (IQR)	56 (50-60)
Male gender; n (%)	57 (79%)
Main reason for LT; n (%)	
Alcoholic cirrhosis	32 (44%)
Hepatocellular carcinoma	22 (31%)
Chronic liver disease non alcoholic non viral	7 (10%)
Primary biliary cholangitis	5 (7%)
Viral hepatitis/ cirrhosis	4 (6%)
Caroli disease/ repeated colangitis	2 (3%)
Iatrogenic ATTR amyloidosis[1], n (%)	21 (29%)
Neurological symptoms, n	20
Cardiovascular symptoms, n	8
Gastrointestinal symptoms, n	10
Urologic symptoms, n	3
Ophalmologic symptoms/ signs, n	2
Renal manifestations, n	2
Diabetes mellitus or other potential cause for peripheral neuropathy; n (%)	33 (46%)
Hypertension; n (%)	28 (39%)
Chronic kidney disease; n (%)	28 (39%)
Atrial fibrillation /flutter; n (%)	6 (8%)
Other supraventricular arrhythmias/ tachycardia	0
Ventricular tachycardia	0
Significant conduction changes[2]; n (%)	1 (1%)

Pacemaker implantation, n (%)	2 (3%)
Probable heart failure[3]; n (%)	10 (14%)
Death; n (%)	32 (44%)

[1]Symptoms could be cumulative.

[2] Second degree Mobitz II or third degree atrioventricular block; symptomatic sinus node disease or another general indication for pacemaker implantation.

[3] Defined as signs or symptoms compatible with heart failure.

Table 2 - Electrocardiographic changes during follow-up

	Baseline (n= 47)	2 years (n=11)	4 years (n= 35)	6 years (n=40)	8 years (n=23)	10 years (n=4)	p
PR interval (ms); mean ± SD	61 ± 29	158 ± 21	173 ± 28	172 ± 29	181 ± 42	154 ± 23	0.003
QRS interval (ms); mean ± SD	97 ± 15	99 ± 16	96 ± 15	97 ± 16	97 ± 20	95 ± 7	0.330
Sokolow index (mV); mean ± SD	23 ± 6	28 ± 6	20 ± 6	19 ± 7	25 ± 15	20 ± 4	0.019
Maximum voltage in the limb leads (mV); mean ± SD	9 ± 3	11 ± 3	10 ± 3	10 ± 4	11 ± 5	9 ± 4	0.656
Mobitz I second degree AV; n (%)	0	0	0	0	0	0	-
High degree AV block (Mobitz II, 2:1 or third degree AV block); n (%)	0	0	0	0	0	0	-
LBBB; n (%)	1 (2%)	0	0	0	0	0	1.000
Pathological Q waves; n (%)	10 (21%)	1 (9%)	8 (23%)	12 (30%)	6 (26%)	1 (25%)	0.375
Repolarization changes; n (%)	20 (43%)	5 (45%)	10 (29%)	18 (45%)	8 (35%)	0	1.000
Poor R wave progression in the precordial leads; n (%)	10 (21%)	1 (9%)	5 (14%)	7 (18%)	6 (23%)	0	1.000

The last column compares the baseline means or proportions to those at 6 years (given that those were the time points with more observations), using paired-sample t test or related-samples McNemar test, respectively.

Legend: AV – atrioventricular; LBBB- left bundle branch block.

Table 3 - Echocardiographic evaluation

Echocardiographic parameters	**Baseline TTE (n= 64)**	**Repeated TTE (n= 26)**
Maximum left ventricular wall thickness (mm); mean ± SD	11 ± 1	12 ± 2
Increased left ventricular wall thickness; n (%)	22 (34%), 3 moderate and 19 mild	17 (65%), 4 moderate and 13 mild
Increased right ventricular wall thickness; n (%)	0	0
Left ventricular telediastolic diameter (mm); mean ± SD	48 ± 4	42 ± 10
Left ventricular dilatation; n (%)	1 (1,6%)	0
Right ventricular dilatation; n (%)	1 (1,6%)	1 (3,8%)
Left ventricular systolic function; n (%)		
- **Normal**	63 (98,4%)	26 (100%)
- **Mildly compromised**	1 (1,6%)	0
- **Moderately compromised**	0	0
- **Severely compromised**	0	0
Compromised right ventricular systolic function; n (%)	0	0
Significant valvular disease; n (%)	1 (1,6%)	1 (3,8%)
Left atrial dilatation; n (%)	31 (48%)	16 (62%)
Granular appearance of the left ventricular walls; n (%)	0	0
Pulmonary artery systolic pressure (mmHg); mean ± SD	32 ± 8	25 ± 6

Dilated inferior vena cava and/or with decreased inspiratory collapse; n (%)	2 (3%)	1 (3,8%)
Pericardial effusion; n (%)	1 (1,6%)	0

Continuous variables are presented as mean ± standard deviation (SD).

The interval between the first and second echocardiogram was on average of 61 ± 32 months.

Table 4 - ProBNP values during follow-up

Baseline	2 years	4 years	6 years	8 years	10 years
263	127	139	130	335	125
(102; 789)	(65-275)	(91; 365)	(67; 487)	(139; 802)	(76; 2645)

Values presented as median (quartiles 25; 75), in ng/mL.